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Subject: 2, 4-D information
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Meghan, hopefully the following addresses the issues discussed earlier today. LT

▶ 2,4-Dichlorophenoxyacetic acid (2,4-D) is an alkylchlorophenoxy herbicide. 2,4-D is well absorbed orally, undergoes limited metabolism, and is eliminated quickly from the body primarily unchanged in the urine by active saturable renal transport. The observed dose-dependent, non-linear pharmacokinetics of 2,4-D is primarily due to the saturation of this renal secretory transport system. This saturation results in elevated plasma concentrations of 2,4-D that are associated with toxicity. The main target organ for 2,4-D is the kidney, where the highest tissue levels are found. There is a gender-based difference in the renal clearance of 2,4-D in adult rats; *i.e.,* males show a greater ability to clear 2,4-D relative to females. Additionally, toxicokinetic studies conducted in pregnant rats show that 2,4-D is transferred through maternal milk to the pups. Due to a limited capacity to excrete organic acids, the dog is more sensitive to the effects of 2,4-D than the rat with respect to repeated dosing. Based on data obtained from the open literature, the calculation of relevant pharmacokinetic parameters for 2,4-D in different species shows that renal clearance, volume of distribution, and plasma half-life of 2,4-D correlate with body weight (allometric scaling) for the mouse, rat, pig, calf, and human but not the dog. The dog shows a lower than expected renal clearance and a longer than expected plasma half-life compared to the other species. The calculated renal clearance in dogs is about an order of magnitude lower than the values expected from allometric scaling for the other species. This is consistent with acute oral toxicity data, which show that the NOAEL in the dog is about an order of magnitude lower than rodent NOAELs.

▶ Looking at the rabbit developmental toxicity study where abortions occurred, these abortions would not be considered an acute effect in this study since they occurred after cessation of dosing on gestation days 21 and 24, and dosing occurred during gestation days 6 through 18.

▶ In the rat developmental toxicity study, the endpoint (increased incidence of skeletal malformations) is considered to be a single dose effect, which occurred at a dose level that exceeds the threshold of saturation of renal clearance.

▶ Short-, intermediate-, and chronic oral endpoints for risk assessment were selected from the extended one-generation reproduction toxicity (EOGRT) study in rats with a NOAEL of 21 mg/kg/day. At the study LOAEL of 55.6/46.7 mg/kg/day, kidney toxicity, manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules, was observed and decreased body weight in pups was observed throughout lactation. Doses for the EOGRT study were selected based on pharmacokinetic data from adults and offspring and is appropriate for short-, intermediate, and long-term durations since the study assessed multiple parameters over several durations of exposure and life stages.